therefore pain relief than analgesic products currently available commercially (i.e., Actiq®, Fentora®; fentanyl buccal tablet, Fentora is a registered trademark of Fentora Cima Labs Inc., Rapinyl®; fentanyl citrate, Rapinyl is a registered trademark of Endo Pharmaceuticals Inc., BEMA Fentanyl). The preliminary data also indicates that Fentanyl SL stays close to T_{max} for 100 minutes translating to pain relief for a longer time.

Example 21

Pharmacokinetic Profile of Fentanyl Sublingual (SL) Spray

In Example 21, a five-treatment, five-sequence, five-period crossover study of Fentanyl SL spray was conducted under fasted conditions in up to 70 healthy subjects. The objectives were to determine the pharmacokinetics of five difference doses (Part A), and to assess the impact of temperature and pH in the oral cavity on the relative bioavailability at a fixed dose (Part B). Healthy subjects had to meet pre-specified eligibility criteria. Plasma samples were obtained at time points of 0, 5, 10, 20, 30, 40 min, 1, 1.25, 1.5, 2, 4, 6, 8, 10, 12, 16, 24 and 36 h post-dose and analyzed for fentanyl using a validated LC-MS-MS procedure.

53 subjects were enrolled in part A. Administration of Fentanyl SL spray was dose-proportional over the 100 mcg to 800 mcg dose ranges. Fentanyl concentrations increase rapidly following administration, being above the LLOQ within 5 minutes, reaching 60.6% of the peak plateau by 10 minutes and 86.6% of the peak plateau by 20 minutes post dose. Fentanyl concentrations showed a relatively long plateau about the peak value (>80% of Cmax) that lasted approximately 2 hours.

14 subjects were enrolled in part B. Varying the pH and temp of the oral cavity did not affect the PK profile. No SAEs were noted. AEs were observed in 31 subjects in part A. 46 were probably related to study treatment, and 29 were possibly related. During part B, AEs were observed in 9 subjects. 7 were probably related to study treatment, and 17 were possibly related. AEs were emesis or nausea.

The results of this study support the rationale for assessing efficacy in patients with breakthrough pain. The dose proportionality supports a rationale for predictable dosing favorable for titration.

Example 22

Comparative Bioavailability of Fentanyl Sublingual (SL) Spray, IV Fentanyl Citrate and Actiq®

In Example 22, a Single-Dose, Open-Label, Randomized, Three-Period, Three-treatment crossover study with a washout period of at least seven days between study periods was conducted at a phase I contract clinic under good clinical practice guidelines. 40 healthy volunteers were enrolled, having met pre-specified eligibility criteria. Subjects received a single dose of Fentanyl SL spray 400 mcg, Actiq® 400 mcg lozenge, and fentanyl citrate 100 mcg by IV injection over 5 minutes in 3 separate treatment periods. Plasma samples were obtained at time points of 0, 5, 10, 20, 30, 40 min, 1, 1.25, 1.5, 2, 4, 6, 8, 10, 12, 16, 24 and 36 h post-dose and analyzed for fentanyl using a validated LC-MS-MS procedure.

The results showed that compared to intravenous administration, the median value for absolute bioavailability of Fentanyl SL spray was 60.8%; bioavailability of Actiq® was 46.6%. The median value for relative bioavailability of Fentanyl SL Spray to that of Actiq® was 135%. Systemic absorption of Fentanyl SL was more rapid than Actiq. Subjects were monitored for any adverse events. AEs were reported in 15 of the 40 subjects. All of the AEs were mild. Two of the AEs were probably related to the study drug (both were sublingual burning at 400 mcg). Three of the AEs were possibly related to the study treatment (headache, dizziness, and dry throat all reported at 400 mcg).

The results of this study support the rationale for assessing efficacy in patients with breakthrough pain.

Many other variations of the present invention will be apparent to those skilled in the art and are meant to be within the scope of the claims appended hereto, including but not limited to the particular unit dose or bi-dose devices and the particle size range of fentanyl produced, as well as other numerical parameters described in the examples, and any combination thereof.

What is claimed is:

1. A sublingual spray formulation comprising a dose of fentanyl which provides one or more mean pharmacokinetic values selected from the group consisting of: AUClast 4.863+/−1.70821 hr*ng/mL, AUCinf 5.761+/−1.916 hr*ng/milliliter, and AUCextrap 10.26+/−5.66%, when administered to humans.

2. A sublingual spray formulation comprising a dose of fentanyl, a free base or a pharmaceutically acceptable salt thereof, which provides a substantially dose proportional mean AUClast based on a mean AUClast of about 4.863+/−1.70821 hr*ng/milliliter when administered to humans.

3. A sublingual spray formulation comprising a dose of fentanyl, a free base or a pharmaceutically acceptable salt thereof, which provides a mean F(AUClast) of about 0.721+/−0.199 ng/milliliter when administered to humans.

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